

BEST AVAILABLE COPY

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 October 2001 (25.10.2001)

PCT

(10) International Publication Number
WO 01/78745 A1

(51) International Patent Classification⁷: **A61K 31/575**,
31/167, A61P 11/06 // (A61K 31/575, 31:167)

(74) Agent: **LEAROYD, Stephanie, Anne**; GlaxoSmithKline,
Corporate Intellectual Property, Two New Horizons Court,
Brentford, Middlesex TW8 9EP (GB).

(21) International Application Number: PCT/GB01/01649

(22) International Filing Date: 11 April 2001 (11.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0009591.9 18 April 2000 (18.04.2000) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **GLAXO
GROUP LIMITED** [GB/GB]; Glaxo Wellcome House,
Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GAVIN, Brian**,
Charles [IE/IE]; GlaxoSmithKline, PO Box 700, Grange
Road, Rathfarnham, 16 Dublin (IE). **GARRETT, Ronique**,
Nichele [US/US]; GlaxoSmithKline, Five Moore Drive,
Research Triangle Park, Durham County, NC 27709 (US).
ROCHE, Trevor, Charles [GB/GB]; GlaxoSmithKline,
Park Road, Ware, Hertfordshire SG12 0DP (GB).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/78745 A1

(54) Title: MEDICAL COMBINATIONS COMPRISING FORMOTEROL AND FLUTICASONE PROPIONATE

(57) Abstract: The present invention is concerned with pharmaceutical formulations comprising a combination of formoterol and fluticasone propionate and the use of such formulations in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

MEDICAL COMBINATIONS COMPRISING FORMOTEROL AND FLUTICASONE PROPIONATE

5 The present invention is concerned with combinations of formoterol and fluticasone propionate, particularly compositions containing a combination of formoterol and fluticasone propionate and the use of such compositions in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

10 Formoterol, i.e. 2'-hydroxy-5'-[(RS)-1-hydroxy-2{[(RS)-p-methoxy- α -methylphenethyl]amino}ethyl]formanilide, particularly its fumarate salt is a well-known adrenoreceptor agonist which is now used clinically in the treatment of bronchial asthma and related disorders.

15 Fluticasone propionate is an anti-inflammatory corticosteroid, described in GB 2088877, and is systematically named S-fluoromethyl-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -propionyloxy-3-oxoandrosta-1,4-diene-17 β -carbothioate. Fluticasone propionate is now used clinically for the treatment of bronchial asthma and related disorders.

20 Although formoterol fumarate and fluticasone propionate may be effective therapies, there exists a clinical need for asthma therapies having potent and selective action and having an advantageous profile of action.

25 Therefore, according to the present invention there is provided a combination of formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and fluticasone propionate or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

30 It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second compound should not be such as to lose the beneficial therapeutic effect of the combination.

35 According to a further aspect of the present invention, there is provided a pharmaceutical formulation comprising formoterol or a pharmaceutically

acceptable salt, solvate, or physiologically functional derivative thereof and fluticasone propionate or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

5 According to a preferred aspect of the present invention, there is provided a pharmaceutical formulation comprising formoterol fumarate and fluticasone propionate, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients. In the most preferred aspect, the above pharmaceutical formulations are suitable for administration by
10 inhalation.

It is to be understood that the present invention covers all combinations of particular and preferred aspects of the invention described herein.

15 As would be appreciated by the skilled person, formoterol includes two asymmetric centres. The present invention includes each isomer of formoterol either in substantially pure form or admixed in any proportions, particularly the (R,R)- isomer. The enantiomers of formoterol have been described previously, for example, in WO98/21175 and US5795564.

20 By the term "physiologically functional derivative" is meant a chemical derivative of formoterol or fluticasone propionate having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional
25 derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids. Pharmaceutically acceptable acid addition salts include but are not limited to those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic,
30 fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic, isethionic, and naphthalenecarboxylic, such as 1-hydroxy-2-naphthalenecarboxylic acids.

Pharmaceutically acceptable esters of formoterol or fluticasone propionate may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

5 As mentioned above, both formoterol and fluticasone propionate and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have been described for use in the treatment of respiratory diseases. Therefore, formulations of formoterol and fluticasone propionate and their
10 pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory
15 tract infection and upper respiratory tract disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is
20 indicated, which comprises administration of a therapeutically effective amount of a combination of formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and fluticasone propionate or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The present invention further provides a method for the prophylaxis or
25 treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and
30 fluticasone propionate or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient. In a preferred aspect, there is provided such a method which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising formoterol fumarate and fluticasone
35 propionate, and a pharmaceutically acceptable carrier or excipient. In

particular, the present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

5

In the alternative, there is provided a combination of formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and fluticasone propionate or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In particular, there is provided a pharmaceutical formulation comprising formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (suitably, formoterol fumarate) and fluticasone propionate or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient for use in therapy, particularly for use in the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. In a preferred aspect, the invention is concerned with the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

25

The amount of formoterol and fluticasone propionate, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. As a monotherapy, formoterol fumarate is generally administered to adult humans by aerosol inhalation at a dose of 12mcg or 24mcg twice daily. As a monotherapy, fluticasone propionate is administered to adult humans by aerosol inhalation at a dose of from 100mcg to 1000mcg twice daily, preferably 200mcg to 500mcg.

30

While it is possible for the active ingredients of the combination to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. When the individual compounds of the combination are administered separately, they are generally each presented as a pharmaceutical formulation as described previously in the art.

Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment. It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each component compound, and containing a package insert instructing the patient to the correct use of the invention is a desirable additional feature of the invention.

Hereinafter, the term "active ingredients" means formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, preferably formoterol fumarate, and fluticasone propionate, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

Suitably, the pharmaceutical formulations which are suitable for inhalation according to the invention comprise the active ingredients in amounts such that each actuation provides therapeutically effective dose, for example, a dose of formoterol of 10mcg to 150mcg, preferably 24mcg and a dose of fluticasone propionate of 50mcg to 1.0mg, preferably 100mcg to 500mcg.

The pharmaceutical formulations according to the invention may further include other therapeutic agents for example anti-inflammatory agents such as other corticosteroids (e.g. budesonide, beclomethasone dipropionate, mometasone furoate, or triamcinolone acetonide), or NSAIDs (e.g. sodium cromoglycate,

nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists), or other β_2 -adrenoreceptor agonists (such as salbutamol, salmeterol, fenoterol or terbutaline and salts thereof), or anticholinergic agents (such as ipratropium, or tiotropium).

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredients into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations for inhalation include powder compositions which will preferably contain lactose, and spray compositions which may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas. Suitable aerosol formulations include those described in EP 0372777 and WO93/11743. For suspension aerosols, the active ingredients should be micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the aerosol formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns, for example, 1 to 5 microns.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

5 Capsules and cartridges or for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator may be formulated containing a powder mix of the active ingredients and a suitable powder base such as lactose or starch. In this aspect, the active ingredients are suitably
10 micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the dry powder formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns.

15 Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

20 Preferred unit dosage formulations are those containing a pharmaceutically effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient. Thus, in the case of formulations designed for delivery by metered dose pressurised aerosols, one actuation of the aerosol may deliver half of the therapeutically effective amount such that two actuations are
25 necessary to deliver the therapeutically effective dose.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question. Furthermore, the claimed formulations include bioequivalents as defined by the US Food and
30 Drugs Agency.

For a better understanding of the invention, the following Examples are given by way of illustration.

35

EXAMPLESA: Metered Dose Inhalers

5 Example 1

	Per actuation
formoterol fumarate	24 microgram
fluticasone propionate	200 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

10 The micronised active ingredients are weighed into an aluminium can, 1,1,1,2-tetrafluoroethane is then added from a vacuum flask and a metering valve is crimped into place.

Similar methods may be used for the formulations of Examples 2 and 3:

15 Example 2

	Per actuation
formoterol fumarate	12 microgram
fluticasone propionate	100 microgram
1,1,1,2-Tetrafluoroethane	to 75.0mg

Example 3

	Per actuation
formoterol fumarate dihydrate	6 microgram
fluticasone propionate	125 microgram
1,1,1,2-Tetrafluoroethane	to 37.50mg

B: Dry Powder Inhalers

Example 4

	Per cartridge or blister
formoterol fumarate	24 microgram
fluticasone propionate	200 microgram
lactose Ph. Eur.	to 12.5mg or to 25.0mg

5

The active ingredients are micronised and bulk blended with the lactose in the proportions given above. The blend is filled into hard gelatin capsules or cartridges or in specifically constructed double foil blister packs to be administered by an inhaler such as a Rotahaler, Diskhaler, or Diskus inhaler (each of these being a Trademark of Glaxo Group Limited).

10

Similar methods may be used for the formulations of Examples 5 and 6:

Example 5

15

	Per cartridge or blister
formoterol fumarate	12 microgram
fluticasone propionate	100 microgram
lactose Ph. Eur.	to 12.5mg or to 25.0mg

Example 6

	Per cartridge or blister
formoterol fumarate dihydrate	12 microgram
fluticasone propionate	250 microgram
lactose NF/BP.	to 25.0 mg

10

C: Intranasal

Example 7: Aqueous nasal spray

5

	Quantity ¹ (% w/w)
Fluticasone propionate (micronised)	0.05
formoterol fumarate dihydrate (micronised)	0.006
dextrose anhydrous	5.00
microcrystalline cellulose and carboxymethylcellulose sodium	1.50
phenylethyl alcohol	0.25
benzalkonium chloride solution (50% w/v)	0.04 v/w
polysorbate 80	0.005
purified water	to 100

¹based on 100mg suspension per actuation

Example 8 : intranasal dry powder

	Quantity per blister
formoterol fumarate (micronised)	12 microgram
fluticasone propionate (micronised)	100 microgram
Potato starch NF/BP	to 10 mg

10

15

D: Nebulisers

Example 9

5

	Quantity (mg)
fluticasone propionate (micronised)	0.25
formoterol fumarate (micronised)	0.012
polysorbate 20	0.14
sorbitan monolaurate	0.018
monosodium phosphate dihydrate	18.80
dibasic sodium phosphate anhydrous	3.50
Sodium chloride	9.60
Water for injections	to 2 ml

Claims

- 5 1. A pharmaceutical formulation comprising formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and fluticasone propionate or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
- 10 2. A pharmaceutical formulation comprising formoterol fumarate and fluticasone propionate, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
- 15 3. A pharmaceutical formulation according to claim 1 or claim 2 wherein the formoterol is in the form of (R,R)-formoterol fumarate.
- 20 4. A pharmaceutical formulation according to any of claims 1 to 3 further comprising another corticosteroid, another β_2 -adrenoreceptor agonist and/or an anticholinergic agent.
- 25 5. A pharmaceutical formulation according to claim 4 wherein the other β_2 -adrenoreceptor is salbutamol, salmeterol, fenoterol, terbutaline, or a salt thereof.
- 30 6. A pharmaceutical formulation according to claim 4 wherein the anticholinergic agent is ipratropium or tiotropium.
- 30 7. A pharmaceutical formulation according to any of claims 1 to 6 wherein the amount of formoterol per unit dose is from above 72 to 150 micrograms.
- 35 8. A pharmaceutical formulation according to any of claims 1 to 7 wherein the amount of fluticasone propionate per unit dose is from above 500 micrograms to 1.0mg.

- 5 9. A pharmaceutical formulation according to any of claims 1 to 8 which is suitable for administration by inhalation.
- 10 10. A pharmaceutical formulation according to any of claims 1 to 8 which is suitable for intranasal administration.
- 15 11. A pharmaceutical formulation consisting of formoterol or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof and fluticasone propionate or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and optionally one or more other therapeutic ingredients, and 1,1,12-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof as propellant.
- 20 12. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist and/or an antiinflammatory corticosteroid is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation according to any one of claims 1 to 11.
- 25 13. A method according to claim 11 wherein the clinical condition is a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.
- 30 14. A method according to claim 11 wherein the clinical condition is respiratory tract infection or upper respiratory tract disease.
15. A Rotahaler, Diskhaler or Diskus inhaler containing a pharmaceutical formulation according to any of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International Application No.

PC 17/GB 01/01649

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/575 A61K31/167 A61P11/06 //(A61K31/575,31:167)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 00 48587 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); CLARKE JEREMY GUY) 24 August 2000 (2000-08-24) claims 1-20	1-15
Y	GB 2 088 877 A (GLAXO GROUP LTD) 16 June 1982 (1982-06-16) claims 1,20-24	1-15
Y	WO 98 21175 A (SEPRACOR INC) 22 May 1998 (1998-05-22) claims 19-21	1-15
Y	US 5 795 564 A (MORLEY JOHN ET AL) 18 August 1998 (1998-08-18) abstract	1-15
	--- -/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

8 August 2001

Date of mailing of the international search report

04/09/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International Application No
PC17/GB 01/01649

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	O'CONNOR B J: "COMBINATION THERAPY" PULMONARY PHARMACOLOGY AND THERAPEUTICS, ACADEMIC PRESS, NEW YORK, NY, US, vol. 11, no. 5/6, 1998, pages 397-399, XP000911059 ISSN: 1094-5539 the whole document ----	1-15
Y	BOWLER S: "LONG ACTING BETA AGONISTS" AUSTRALIAN FAMILY PHYSICIAN, XX, XX, vol. 27, no. 12, December 1998 (1998-12), pages 1115,1117-1118, XP000973076 the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01649

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0048587 A	24-08-2000	AU 2911500 A	04-09-2000
GB 2088877 A	16-06-1982	AT 395428 B	28-12-1992
		AT 17084 A	15-05-1992
		AT 401521 B	25-09-1996
		AT 34491 A	15-02-1996
		AT 395427 B	28-12-1992
		AT 67481 A	15-05-1992
		AT 395429 B	28-12-1992
		AT 203186 A	15-05-1992
		AU 544517 B	06-06-1985
		AU 6729881 A	20-08-1981
		BE 887518 A	13-08-1981
		BG 60700 B	29-12-1995
		CA 1201114 A	25-02-1986
		CA 1205464 C	03-06-1986
		CH 644615 A	15-08-1984
		CH 651307 A	13-09-1985
		CZ 9104034 A	16-03-1994
		CY 1291 A	18-10-1985
		DE 3105307 A	10-12-1981
		DE 3153379 C	19-11-1992
		DK 62381 A,B,	16-08-1981
		ES 499394 D	01-09-1982
		ES 8207194 A	01-12-1982
		ES 509539 D	01-04-1983
		ES 8305379 A	01-07-1983
		ES 518161 D	16-01-1984
		ES 8402317 A	16-04-1984
		ES 524985 D	01-01-1985
		ES 8502447 A	01-04-1985
		ES 532055 D	16-10-1985
		ES 8600936 A	16-02-1986
		FI 810444 A,B,	16-08-1981
		FR 2477156 A	04-09-1981
		FR 2485542 A	31-12-1981
		GB 2137206 A,B	03-10-1984
		HK 58385 A	16-08-1985
		IE 51394 B	24-12-1986
		IE 51395 B	24-12-1986
		IT 1170717 B	03-06-1987
		JP 1488353 C	23-03-1989
		JP 56138200 A	28-10-1981
		JP 63037120 B	22-07-1988
		KE 3526 A	07-06-1985
		KR 8500969 B	02-07-1985
		MX 9202717 A	30-06-1992
		MY 75785 A	31-12-1985
		NL 84649 C	
		NL 8100707 A,B,	16-09-1981
		NZ 196260 A	30-11-1983
		PH 24267 A	29-05-1990
WO 9821175 A	22-05-1998	AU 722859 B	10-08-2000
		AU 5175598 A	03-06-1998
		EP 0938467 A	01-09-1999
		US 6040344 A	21-03-2000

Internal Application No
PCI/GB 01/01649

Form PCT/ISA/210 (patent family annex) (July 1992)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.